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Caffeine effects on VO_{2MAX} test outcomes investigated by a placebo perceived-as-caffeine design

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Abstract

Background: Ergogenic effects of caffeine (CAF) ingestion have been observed in different cycling exercise modes, and have been associated with alterations in ratings of perceived exertion (RPE). However, there has been little investigation of maximal oxygen uptake (VO_{2MAX}) test outcomes. **Aim:** This study aimed to verify whether CAF may reduce RPE, thereby improving maximal incremental test (MIT) outcomes such as VO_{2MAX}, time to exhaustion and peak power output (W_{PEAK}). **Methods:** Nine healthy individuals performed three MITs (25 W/min until exhaustion) in a random, counterbalanced fashion after ingestion of CAF, placebo perceived as caffeine (PLA), and no supplementation (baseline control). VO_2 was measured throughout the test, while RPE was rated according to overall and leg effort sensations. The power output corresponding to submaximal (RPE = 14 according to the 6–20 Borg scale) and maximal RPE was recorded for both overall ($O\text{-}RPE_{14}$ and $O\text{-}RPE_{MAX}$) and leg RPE ($L\text{-}RPE_{14}$ and $L\text{-}RPE_{MAX}$). **Results:** VO_{2MAX} did not change significantly between MITs; however, CAF and PLA increased time to exhaustion (↑ ~18.7% and ~17.1%, respectively; $p < .05$) and W_{PEAK} (↑ ~13.0% and ~11.8%, respectively; $p < .05$) when compared with control. When compared with control, CAF ingestion reduced submaximal and maximal overall and leg RPEs, the effect being greater in maximal (likely beneficial in $O\text{-}RPE_{MAX}$ and $L\text{-}RPE_{MAX}$) than submaximal RPE (possibly beneficial in $O\text{-}RPE_{14}$ and $L\text{-}RPE_{14}$). Similar results were found when participants ingested PLA. **Conclusions:** Compared with control, CAF and PLA improved MIT performance outcomes such as time to exhaustion and W_{PEAK}, without altering VO_{2MAX} values. CAF effects were attributed to placebo.

Keywords

Cycling exercises, performance, ratings of perceived exertion, VO_{2MAX}, placebo effects

Introduction

Caffeine (CAF) is an ergogenic that improves performance and alters physiological and psychological responses during exercise (Goldstein et al., 2010; Sökmen et al., 2008). Regarding psychological effects, CAF is suggested to reduce the sensation of fatigue during exercise (Plaskett and Cafarelli, 2001; Stadheim et al., 2013). For example, Astorino et al. (2012) showed that CAF ingestion decreased the time to complete a 10 km cycling time trial in both endurance-trained and untrained individuals, probably due to the decreased ratings of perceived exertion (RPE) and leg pain sensation. In addition, Desbrow et al. (2012) and Bortolotti et al. (2014) showed that CAF increased performance either in a work-matched constant exercise or in a 20 km cycling time trial. Despite no apparent effects on RPE, participants performed more work at the same RPE, thereby confirming the likely beneficial effect of CAF on RPE responses. Interestingly, these effects may be present at severe, rather than mild intensities, as CAF supplementation affected RPE during constant workload exercise at 80%, but not at 50%, of the maximal oxygen uptake (VO_{2MAX}) (Bell and McLellan, 2003).

Effects of CAF supplementation on RPE responses and exercise performance have been reported in work-matched constant cycling and cycling time trials (Astorino et al., 2012), but there has been less investigation of effects on incremental VO_{2MAX} test outcomes. A few

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studies investigating cycling maximal incremental tests (MIT) have found controversial results after CAF intake, as one found unimproved performance despite the increased VO_{2MAX} (Dodd et al., 1991), while another observed improvements in performance (Flinn et al., 1990). No VO_{2MAX} measures were reported in this later study. Importantly, no RPE measures were reported in those MIT studies, so it was not possible to assume that changes in MIT outcomes such as VO_{2MAX} and time to exhaustion were further related to changes in RPE. In this regard, whether CAF may improve VO_{2MAX} and time to exhaustion during an MIT through a reduced RPE at high, rather than mild, intensities still requires confirmation.

Possible CAF effects on incremental VO_{2MAX} tests may be of interest, as outcomes derived from MIT have been used in clinical diagnosis and endurance training programs (Bentley et al., 2007; Shephard, 1984). For example, higher VO_{2MAX}, time to exhaustion and peak power output (W_{PEAK}) values during an MIT have been positively associated with higher endurance capacity (Bentley et al., 2007; Stringer, 2010). Therefore, the aim of this study was to determine whether CAF supplementation would reduce sensation of fatigue (i.e. RPE) during MIT, thus allowing the attainment of a greater VO_{2MAX}, W_{PEAK} and time to exhaustion. The hypothesis was that CAF would reduce RPE, thus eliciting greater MIT outcomes (i.e. VO_{2MAX}, W_{PEAK} and time to exhaustion).

Materials and methods

Participants and ethics procedures

Nine healthy, physically active individuals (26.4 $\pm$ 4.8 years, 77.6 $\pm$ 12.1 kg, 171.7 $\pm$ 6.9 cm and 13.2 $\pm$ 6.0% of body fat) volunteered to take part in this study. The participants were nonsmokers, free from any neuromuscular limitation or cardiopulmonary dysfunction, and used no medications that could interfere with dependent variables when the study was conducted. Importantly, except for coffee drinks, they did not drink tea, cola, chocolate or any other source of caffeine. Although they consumed caffeine in the form of coffee drinks, three participants drank less than 250 ml of coffee a day, three drank less than 100 ml a day, and three did not drink coffee. Thus, assuming $\sim$44.5 mg of caffeine in each 100 ml of coffee drink consumed (Fitt et al., 2013), participants who consumed coffee drinks ingested less than 120 ($n = 3$) or 44.5 ($n = 3$) mg of caffeine a day. The experimental procedures, risks and benefits of the study were explained before an informed consent form was obtained. This study conformed to the Declaration of Helsinki and was approved by the Ethics Committee board of the University where this study was conducted (Process 0023.0.342.000-10).

Experimental design

The experimental design consisted of: a) a preliminary visit to familiarize participants with an MIT and to measure body composition according to standard procedures International Society for Advancement in Kinanthropometry (ISAK) (Jackson and Pollock, 1978); b) a control MIT with neither CAF nor placebo (PLA) ingestion (baseline control session); c) an MIT 60 min after the CAF intake; and d) an MIT 60 min after the PLA intake (sucrose). After the preliminary familiarization session, participants performed sessions 2, 3 and 4 in a randomized, counterbalanced order. The tests were performed with a 4–7-days wash-out period between them in order to remove any residual effects of fatigue and substance ingested. Participants habitually used a bicycle as a mode of transport, so all the MITs were performed on a road cycling bike (Gyant®, USA) prepared with seat and pedals for non-cyclists, and coupled to a cycle simulator (Computrainer, Racer Mate®, USA). Performance and cardiopulmonary measures were continuously obtained throughout the tests, while overall and local RPE were obtained at regular intervals. Participants were instructed to avoid intense physical exercise, coffee drinks, alcohol or any stimulant beverages for at least 24 h before the experimental sessions. Specifically to control for effects of carbohydrate (CHO) loading on caffeine supplementation, we strongly recommended that they maintain their habitual diet ($\sim$60% CHO, $\sim$20% protein and $\sim$20% fat) while they were committed to the study.

Procedures and measurements in MIT

After 6 min warming up at 100 W with a pedal cadence fixed at 80 rpm, the MIT progressed with 25 $W \cdot min^{-1}$ increments until exhaustion. Verbal encouragement was provided by a researcher unaware of the substance under investigation, to ensure the attainment of maximal effort. The gas exchange was continuously recorded on a breath-by-breath mode, by using a mask attached to an open circuit gas analyzer (Quark b2, Cosmed, Italy), which provided ventilation (VE), oxygen uptake (VO_2) and carbon dioxide production (VCO_2) measures. The expired air volume was measured through a bi-directional flow sensor, calibrated before each test using a 3 L air syringe. A zirconium sensor analyzed the expired fraction of O_2, while the end tidal CO_2 was analyzed by infrared absorption. Both sensors were calibrated automatically before each test with a known O_2 (20.9%) and CO_2 (5%) concentration. The breath-by-breath VE, VO_2 and VCO_2 data recorded throughout the MIT were averaged to 10 s intervals; thereafter, the VO_{2MAX} was determined according to the traditional plateau criterion, an increase $\leq$150 $ml \cdot min^{-1}$ in VO_2 (Taylor et al., 1955). The W_{PEAK} was considered as the highest power output recorded in the test.

Overall and local (legs) RPE were obtained using the 6–20 point Borg scale (Borg, 1982) at the end of each stage. Participants were oriented to rate their overall RPE (O-RPE) according to body discomfort (i.e. breathlessness, cardiac work and body temperature), whereas leg RPE (L-RPE) was rated as muscle discomfort (Hampson et al., 2001). Importantly, we oriented them to rate muscular

hardness rather than muscular pain during exercise. Then, as CAF supplementation may differently affect RPE according to the exercise intensity (Bell and McLellan, 2003), we recorded the power output corresponding to submaximal and maximal RPE (RPE_{MAX}) when comparing conditions (baseline control, CAF and PLA). Thus, we used the power output recorded when the RPE was rated as 14 (O-RPE_{14} and L-RPE_{14}) as well as when it was maximal (O-RPE_{MAX} and L-RPE_{MAX}) on the Borg scale.

Caffeine and placebo perceived as caffeine supplementation

Experimental tests with CAF or PLA were performed 60 min after the ingestion of 6 mg·kg^{-1} body weight of caffeine or a sucrose-based substance (placebo). Both substances were formulated in opaque capsules with identical texture, odorless and tasteless. Importantly, participants were told that the study was aiming to investigate the reproducibility of CAF as a potential supplementation to improve physical performance, and that they would ingest a caffeine capsule in both sessions. Thus, participants were provided with positive information about potential effects of CAF supplementation to enhance performance. It is important to note that studies have argued that the use of double-blind designs is a possible source of bias in clinical trials and sports nutrition studies (Kirsch and Weixel, 1988; Saunders et al., 2016, since uncovering a PLA intervention correctly during a clinical trial could negatively affect performance outcomes in physical tests (Saunders et al., 2016). Therefore, participants ingested PLA perceived as CAF, because the expectation of ingesting CAF, rather than its physiological effects in isolation, could affect subjective responses such as RPE (Domotor et al., 2015; Kirsch and Weixel, 1988). Similarly to designs reported elsewhere, we informed participants about the presence of a PLA supplementation only when they had concluded their participation in the study (Bell et al., 2001; Duncan et al., 2009; Hadjicharalambous et al., 2006). An investigator, who was unaware of the substance used, provided verbal encouragement during all MIT exercises.

Data analysis

Data were analyzed by two researchers who were not involved in data collection. The data was first checked for Gaussian distribution by applying the Shapiro–Wilk test. Responses obtained in baseline control and CAF- and PLA-supplemented MIT, such as time to exhaustion, W_{PEAK} and VO_{2MAX}, were compared using a repeated-design mixed model with supplementation as fixed factor and individuals as random factor. The Bonferroni test was used as a multiple comparisons correction, always when F values were significant. Power output values corresponding to both submaximal (O-RPE_{14} and L-RPE_{14}) and maximal effort level (O-RPE_{MAX} and L-RPE_{MAX}) were analyzed using a 3 × 2 × 2 repeated-design mixed model, with supplementation (baseline control vs. CAF vs. PLA), site of RPE measurement (leg vs. overall) and effort level (RPE_{14} and RPE_{MAX}) as fixed factors, while participants were the random factor. In addition, power output results at different RPEs were analyzed according to the magnitude-based inference (Hopkins et al., 2009), and the qualitative probabilities were defined as: <0.5% almost certainly not; <5% very unlikely; <25% unlikely, probably not; 25–75% possibly, possibly not; >75% likely, probably; >95% very likely; >99.5% almost certainly. Power of analysis was calculated when results reached statistical significance. Statistical significance was set at 5% in all analyses, having been performed in a Statistical Package for the Social Sciences (SPSS) package (version 19).

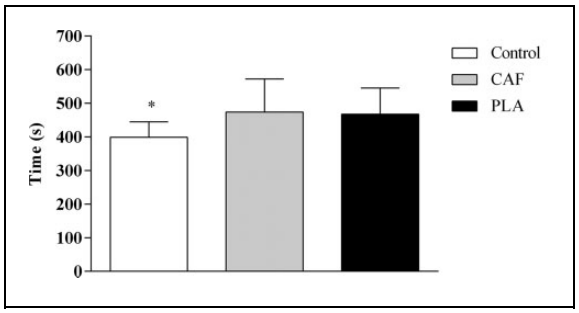

Figure 1. Time-to-exhaustion in maximal incremental test (MIT). *Different from caffeine and placebo. CAF: caffeine ingestion; PLA: placebo ingestion.

Results

There was no significant difference ($p > .05$) in VO_{2MAX} values between CAF (VO_{2MAX} of 43.3 ± 4.7 ml.kg^{-1}.min^{-1}), PLA (VO_{2MAX} of 43.6 ± 5.0 ml.kg^{-1}.min^{-1}) and baseline control session (VO_{2MAX} of 42.2 ± 4.6 ml.kg^{-1}.min^{-1}).

Performance outcomes indicated a supplementation main effect for time to exhaustion ($p = .007$; power = 0.81) and W_{PEAK} ($p = .006$; power = 0.81). Multiple comparisons showed that time to exhaustion was significantly improved in both CAF (↑ ~ 18.7%; $p = .017$) and PLA (↑ ~ 17.1%; $p = .011$) supplementation when compared with control (Figure 1). Accordingly, W_{PEAK} improved significantly in CAF (↑ ~ 13.0%; $p = .017$) and PLA (↑ ~ 11.8%; $p = .011$) supplementation in relation to control (Figure 2). No significant difference was detected between CAF and PLA supplementation.

Regarding overall RPE responses, an effort level main effect was detected, since power output recorded when RPE was maximum (i.e. RPE_{MAX}) was greater than RPE_{14} ($p = .015$; power = 0.53). However, neither supplementation main effect ($p = .91$; power = 0.49) nor effort level by supplementation interaction effect was observed ($p = .58$; power = 0.30). Thus, neither CAF nor PLA induced significant differences ($p > .05$) in submaximal and maximal effort levels during MIT when compared with baseline control: O-RPE_{14} and O-RPE_{MAX}, respectively (Table 1). Accordingly, when compared with control, neither

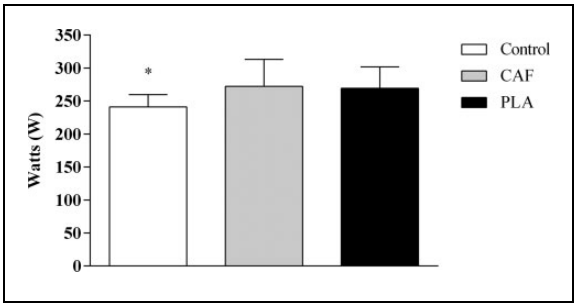

Figure 2. Peak power output in maximal incremental test (MIT). *Different from caffeine and placebo. CAF: caffeine ingestion; PLA: placebo ingestion.

Table 1. Power output at submaximal and maximal RPE during supplemented and control MIT.

	Submaximal	Maximal
Overall		
Control	201.4 ± 34.4	258.3 ± 28.0
CAF	194.9 ± 49.4	277.8 ± 47.5
PLA	201.1 ± 25.5	272.2 ± 31.7
Legs		
Control	184.3 ± 24.2	258.3 ± 28.0
CAF	189.2 ± 36.2	277.8 ± 47.5
PLA	189.5 ± 21.2	272.2 ± 31.7

Submaximal RPE was rated as 14 on the Borg's scale.
CAF: caffeine ingestion; PLA: placebo ingestion. Data are presented in mean ± SD.

CAF nor PLA significantly altered L-RPE in submaximal and maximal effort levels in MIT: L-RPE_{14} and L-RPE_{MAX}, respectively. Both overall and leg RPE rated throughout the different MITs are depicted in Figure 3(a) and (b).

However, magnitude-based inference analysis showed "possibly and likely" beneficial effects of both supplementations when RPE was rated in submaximal and maximal effort levels. Thus, Table 2 shows that when compared with control at submaximal RPE level, O-RPE_{14} and L-RPE_{14} possibly benefited from CAF and PLA supplementation. Accordingly, relative to control at maximal effort, O-RPE_{MAX} and L-RPE_{MAX} further likely benefited from CAF and PLA supplementation.

Discussion

The main finding of the present study was that CAF supplementation improved performance outcomes in MIT when compared with the control, but not with the PLA, condition. Such an improvement in performance outcomes occurred without alterations in VO_{2MAX} responses, likely due to a reduced RPE at maximal effort levels. Results observed with CAF supplementation were seemingly attributable to placebo effects, as participants also improved MIT performance outcomes when they perceived PLA as CAF. These results address important practical implications for MIT used in laboratory and clinical routines.

Table 2. Magnitude-based inferences for power output corresponding to different RPEs in supplemented and control MIT.

	Caffeine vs. control	Placebo vs. control
O-RPE_{14} (Watts)		
Harmful	Unlikely	Possibly
Trivial	Unlikely	Unlikely
Beneficial	Possibly	Possibly
L-RPE_{14} (Watts)		
Harmful	Unlikely	Unlikely
Trivial	Unlikely	Unlikely
Beneficial	Possibly	Possibly
RPE_{MAX} (Watts)		
Harmful	Unlikely	Unlikely
Trivial	Very unlikely	Very unlikely
Beneficial	Likely	Likely

Qualitative probabilities defined by Hopkins (2006) as follows: <0.5%, almost certainly not; <5%, very unlikely; <25%, unlikely, probably not; 25–75%, possibly, possibly not; >75%, likely, probably; >95%, very likely; >99.5%, almost certainly (Hopkins, 2006).

When compared with the control condition, participants perceived less exertion when ingesting CAF, as they had a 75% chance of benefiting from CAF supplementation at maximal effort levels (i.e. likely beneficial effect according to the magnitude-based inference analysis). Some have supported the notion that CAF may reduce the effort sensation during exercise through different mechanisms (Backhouse et al., 2011; de Morree et al., 2014; Kalmar and Cafarelli, 2004b; Plaskett and Cafarelli, 2001). de Morree et al. (2014) observed that ingestion of CAF reduced the primary motor cortex (Cz position) activation necessary to maintain a submaximal isometric knee extension at the very beginning of exercise, and this lowered Cz activation was correlated with a reduced RPE throughout the exercise. The authors hypothesized that the increased cortical excitability triggered by CAF would have required less excitatory input from Cz (and other motor cortex areas such as premotor cortex) at the same motor output, thus reducing the level of corollary discharges driven to RPE (de Morree et al., 2014; Marcora, 2009). Furthermore, an earlier study (Plaskett and Cafarelli, 2001) had found an attenuated force sensation at the beginning of a similar isometric knee extension exercise performed after CAF ingestion, perhaps suggesting a reduced activation of peripheral sensory receptors (Kalmar and Cafarelli, 2004a). Regardless of the exact mechanism of action, whether centrally located in the central nervous system or at the periphery, increments in exercise performance with CAF supplementation could be related to a lowered RPE. However, comparisons between CAF and PLA have indicated that CAF improved performance outcomes in MIT due to a likely placebo effect, rather than those mechanisms traditionally suggested.

Actually, an interesting finding was obtained with the PLA condition, as we observed that PLA improved MIT

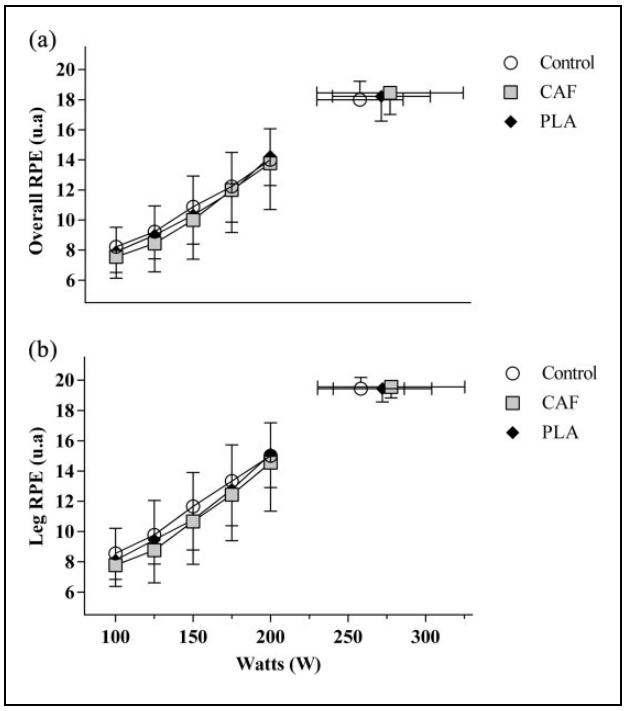

Figure 3. Overall RPE (a) and leg RPE (b) throughout the maximal incremental test (MIT). CAF: caffeine ingestion; PLA: placebo ingestion.

performance and reduced RPE, similarly to CAF. Somehow, PLA perceived as CAF may have changed MIT outcomes (i.e. performance and RPE responses) through similar cerebral mechanisms to those suggested for CAF. For example, the positive expectation and belief in an effective treatment are thought to induce a reduced activation in areas involved in cognitive processes, such as dorsolateral prefrontal cortex, primary somatosensory cortex, insular cortex, and anterior cingulate cortex (Benedetti et al., 2011; Ellingsen et al., 2013; Sevel et al., 2015), probably as a consequence of enhanced corticospinal excitability (Fiorio et al., 2014). Therefore, as proposed for CAF ingestion (de Morree et al., 2014; Marcora, 2009), cortical alterations in motor areas with PLA ingestion may have led to fewer corollary discharges driven to RPE generation, thus making possible a greater motor output (i.e. MIT performance) for the same effort sensation.

Furthermore, qualitative analysis based on the magnitude-based inferences may indicate that the belief or expectation of having a beneficial treatment, rather than the physiological effects of caffeine in isolation, may have driven effects on RPE responses in the present study. Although traditional statistics has not detected CAF effects on RPE responses, qualitative analysis showed a possible (25% to 75%) and likely (75%) chance of CAF and PLA effects on submaximal and maximal effort levels, respectively. It is important to note that, unlike a traditional double-blind design, we led participants to believe that they would ingest caffeine in both CAF and PLA conditions, so that they were not in a position to contrast placebo with caffeine; that is, no contrast between supplementations would make sense, as both supplementations were believed to contain the same substances. Hence, the belief that CAF would enhance performance in our PLA intervention may have induced an increase in the participants' self-efficacy, thereby lowering RPE and increasing MIT performance (Beedie et al., 2007; Saunders et al., 2016). Other studies are required to confirm these results in individuals with characteristics different from those investigated here, as placebo responsiveness may vary between individuals (Foad et al., 2008).

Unexpectedly, performance in MIT in both CAF and PLA supplementation was improved, regardless of alterations in VO_{2MAX} values. These results are contrary to those found in an earlier study reporting an unimproved MIT performance despite the increased VO_{2MAX} values after CAF ingestion (Dodd et al., 1991). In the present study, we found that neither CAF nor PLA increased VO_{2MAX} in MIT, even though there was a 13.0% and 11.8% increase in W_{PEAK} with CAF and PLA, respectively, when compared with baseline control. With the exception of one participant eliciting a VO_2 plateau above the classical plateau criterion, as the VO_2 plateau occurred between 150 and 200 $mL \cdot kg \cdot min^{-1}$, all participants elicited a true VO_2 plateau at similar values, in all MIT conditions. Hence, these results may challenge the concept that improvements in VO_{2MAX} are the basis for improvements in MIT performance outcomes and, therefore, endurance capacity (Noakes, 1998).

Methodological aspects and implications

Some methodological aspects should be considered. First, we have not used a double-blind design, because we had to deceive participants to make them believe they were receiving CAF in both supplementation conditions. This methodological approach may have overestimated the PLA effect when compared with a typical double-blind design, which lets participants believe they would have a 50% chance of having a real substance or a placebo intervention (Vase et al., 2002). It is important to highlight that some have challenged double-blind design approaches for CAF investigations, as the expectation of ingesting CAF, rather than its physiological effects in isolation, may influence subjective measures such as RPE (Domotor et al., 2015; Kirsch and Weixel, 1988). Therefore, instead of a limitation, this aspect of the experimental design should be considered as a positive feature, since RPE was a key dependent variable of the present study. In addition, the use of a double-control design by having a baseline control and PLA condition strengthened our approach, as we were able to contrast CAF and PLA supplementation with a totally inert condition (i.e. baseline condition).

Two aspects regarding caffeine habituation and diet control should be pointed out. The first has been traditionally debated, as most have argued that habituation to caffeine may interfere with potential ergogenic effects of CAF supplementation. However, this has been apparently a

case of anecdotal rather than scientific evidence, as earlier (Tarnopolsky and Cupido, 2000) and more recent studies (Goncalves et al., 2017) have shown that CAF supplementation affects performance regardless of habituation. Moreover, the fact that we included caffeine users consuming less than 120 mg of caffeine a day does not apparently turn out to be a limitation. In fact, CAF effects may have been potentiated in the present study, since we used non-users ($n = 3$) or users ($n = 6$) consuming low doses of caffeine, thus improving the chances for a true CAF effect according to the habituation hypothesis.

Regarding the diet control, most consensual understanding assumes that changes in muscle glycogen content prior to exercise may affect exercise performance. This understanding supports the notion that low, instead of high, muscle glycogen content prior to an exercise bout may induce alterations (i.e. decrements) in performance, mainly during exercises lasting 60–90 min (Hawley et al., 1997; Thomas et al., 2016). A possible limitation of the present study was that we did not design any particular approach to control for CHO consumption, so that variations in muscle glycogen content may have occurred. However, we oriented participants to maintain their habitual diet ($\sim$60% CHO, $\sim$20% protein and $\sim$20% fat) while participating in the study, and strongly recommended them to avoid intense physical exercise during the 24 h before the test sessions. Thus, while recognizing the importance of diet control in studies involving caffeine, we suggest that eventual variations in muscle glycogen content prior to MIT were unlikely to induce changes in performance, since muscle glycogen stores can be normalized by 24 h of reduced training and adequate food intake (Thomas et al., 2016). In fact, a combination of exhaustive exercise and low-CHO diet in the days preceding the test session is probably a better strategy to induce relevant decreases in muscle glycogen content (Gollnick et al., 1973, 1974).

The results of the present study have practical implications, because we observed that both CAF and PLA supplementation elicited similar improvements in MIT performance, together with a reduced RPE. These results may suggest that PLA is as effective as CAF in improving MIT performance outcomes, while avoiding some possible side effects on the cardiovascular system (such as atrial fibrillation and supraventricular tachyarrhythmia), potassium balance, sleepiness quality and gastric comfort/discomfort. Thus, PLA perceived as CAF may be preferable in MIT trials directed to endurance status evaluation and training prescription, if the individuals to be evaluated are highly sensitive to CAF (Ali et al., 2015; Zulli et al., 2016).

In conclusion, the results of the present study showed that, when compared with the control condition, both CAF and PLA supplementation improved MIT performance outcomes such as time to exhaustion and W_{PEAK}, without altering VO_{2MAX} values. Such an MIT performance improvement was probably related to a reduced RPE, mainly at maximal effort levels. The results further suggested that CAF effects were attributable to placebo.

Availability of data and materials

Due to Institutional policy, data is available upon reasonable request.

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Authors' contributions

Cayque Brietzke and Ricardo Yukio Asano participated equally in the study.
Study design: CU and FOP
Data collection: FP and FOP
Data analysis: CB, RYA, FRL, PEF and FOP
Writing the manuscript: CB, RYA and FOP
Revising the manuscript: FP, CU, FRL and PEF

Consent for publication and ethical approval

The authors declare that they consent to publication of the manuscript in the present form, this study having been approved by an Institutional Ethics Committee.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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